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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No.	Applicant(s)	
	09/779,791	WOLFF ET AL.	
	Examin r	Art Unit	
	Joseph T Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *7-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application filed February 8, 2001, is a continuation in part of application 09/312,351, filed May 14, 1999.

Applicants' amendment filed May 5, 2003, paper number 15, has been received and entered. Claims 1, 7 and 13 have been amended. Claims 1-13 are pending and currently under examination.

Election/Restriction

Applicant's election with traverse of Group I and the species of a polymer containing a cationic charge (bottom of page 9) in Paper No. 15 is acknowledged. The traversal is on the ground(s) that while the factors defining the differences between the different groups are distinct they are intimately interdependent (middle of page 8). More specifically, Applicants summarize the nature of the invention and argue that for a disulfide bond to be cleaved more rapidly than oxidized glutathione either the disulfide bond has a lower pKa or there is a third free thiol which is sterically constrained. Applicants acknowledge the differences between the limitations however note that at any one time two of the three limitations must be met. Applicants argue that not addressing each of the limitations together would not allow for effective coverage of the invention (bridging pages 8-9). Therefore, Groups I-III and IV-VI should be rejoined. With respect to the election of species, Applicants argue that transduction signals are believed to

operate by a similar mechanism and that a search and references studying any one of the specific signals typically makes reference to others. Applicants' arguments have been fully considered and are found persuasive in part.

With respect to each of the properties recited being interdependent, Examiner agrees but as acknowledged by Applicants, maintains that each property is distinct. Upon consideration of Applicants arguments, the two properties which are not mutually exclusive are lower pKa and being cleaved more rapidly that glutathione. Therefore, Groups I and II are rejoined, as well as Groups IV and V. With respect to a disulfide bond activated by intramolecular attack of a free thiol (Groups III and VI), the claimed compound (and specific methods of use) would be materially and physically different than a compound comprising only a single disulfide bond and does not necessarily meet or require either of the two other limitations.

With respect to the election of species, initially it is noted that there is no art of record wherein all the specific species are set forth or discussed together as discussed by Applicants. However, upon consideration of the potential mechanism for the function of a "transduction signal" Examiner would note that these are not proper species of each other. Rather, the restriction should set forth the groups as linking claims and that each of the different embodiments are linked by a potentially common function of acting as a transduction signal. Applicant had elected a polymer containing a cationic charge (page 9). It is noted that one kind of polymer would be a protein and further, each of the specific proteins listed in claims 2-4 would be considered species of a protein. Because there is only three species, Examiner would

agree that it would not be an undue burden to search and examine each of the three specific species of protein recited in the claims. Therefore, the species election is withdrawn.

For clarity of record the revised restriction requirement is set forth below. The restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-6 and 13, drawn to a compound for inserting into an organism comprising (a) a disulfide bond which is cleaved more rapidly that oxidized glutathione and which one of the constituent thiols has a lower pKa than glutathione and (b) a transduction signal, classified in class 514, subclass 1, class 536, subclass 23.1, 24.1.

II. Claims 1-6 and 13, drawn to a compound for inserting into an organism comprising (a) a disulfide bond which is activated by intramolecular attack from a free thiol and (b) a transduction signal, classified in class 514, subclass 1, class 536, subclass 23.1, 24.1.

III. Claims 7-12, drawn to a process for delivering a compound having a labile disulfide bond wherein the compound comprises (a) a disulfide bond which is cleaved more rapidly that oxidized glutathione and which one of the constituent thiols has a lower pKa than glutathione and (b) a transduction signal, classified in class 514, subclass 1, class 536, subclass 23.1, 24.1.

IV. Claims 7-12, drawn to a process for delivering a compound having a labile disulfide bond wherein the compound comprises (a) a disulfide bond which is

activated by intramolecular attack from a free thiol and (b) a transduction signal, classified in class 514, subclass 1, class 536, subclass 23.1, 24.1.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II as well as III and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different compounds comprise different types of disulfide linkages. A disulfide bond which is activated by intramolecular attack from a free thiol does not have to be more rapidly oxidized than oxidized glutathione or be constructed from a constituent thiol having a lower pKa than glutathione. Additionally, the methods of delivery comprise the use of different compounds which comprise different types of disulfide linkages. A disulfide bond which is activated by intramolecular attack from a free thiol does not have to be more rapidly oxidized than oxidized glutathione or be constructed from a constituent thiol having a lower pKa than glutathione.

Inventions I-II and III-IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the compositions can be used in methods for the delivery to cells

in culture. Additionally, the process can be practiced with compounds which do not have disulfide bonds or with disulfide bonds with different properties.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Claims 1-13 are pending. Applicants had elected Group I, claims 1-6 and 13 (which has been rejoined with group II), therefore, claims 7-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 15. Claims 1-6 and 13 are currently under examination as they are drawn to a compound for inserting into an organism comprising (a) a disulfide bond which is cleaved more rapidly that oxidized glutathione and which one of the constituent thiols has a lower pKa than glutathione and (b) a transduction signal wherein the signal is a polymer containing a cationic charge.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any

amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Applicant's attention is directed to the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). The specification contains specific sequences which are not identified by SEQ ID NOs, for example page 26, lines 4-7 and 26, or page 35, lines 13-14. Each specific sequences set forth in the specification must be identified by the appropriate sequence identifier.

Appropriate correction is required.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". Specifically, the recitation of "labile under mammalian intracellular physiological conditions" is considered new matter. Applicants have not pointed to the specific portion of the specification for support of this new amendment, and upon review of the specification Examiner can not find literal support for the recitation nor figurative support teaching the metes and bounds encompassed by this embodiment.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claim 1 is also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly

conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure" (emphasis added).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 1 is indefinite in the recitation of "mammalian intracellular physiological conditions". The specification provides no specific definition of the conditions encompassed by this term nor methods and guidance for determining what these conditions encompass. It is noted that the specification supports the intended use of the compound in a mammal, however it fails to provide support for the use of the methods intracellularly and what conditions exist intracellularly in a mammal. Dependent claims 2-5 and 13 are included in the basis of the

rejection because they fail to further clarify the nature of the physiological condition and only further define the compounds attached to the product.

Claim 13 recites the limitation "wherein the molecule" in reference to claim 1. There is insufficient antecedent basis for this limitation in the claim. It is noted that the claim has been amended from 'the compound' which is supported by claim 1 to 'the molecule' which is not recited in claim 1. More clearly indicating the relation of the addition of a nucleic acid to the compound of claim 1 or amending claim 1 to indicate that additional molecules besides a disulfide and a transduction signal are present would obviate the basis of the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
> (f) he did not himself invent the subject matter sought to be patented.

Claims 1, 5 and 6 are rejected under 35 U.S.C. 102(a) as being anticipated by Bulaj *et al.* (IDS reference) as evidenced by Szajewski *et al.* (IDS reference).

Bulaj *et al.* teach two disulfide linked peptides, Pti38 and Pti51a. Each peptide contains positive charges and have a lower pKa as a consequence (see page 8968, top of second column). The specific pKa is 8.26 for Pti38 and 8.38 for Pti51a (page 8967, Table 1). Szajewski *et al.* teach that the pKa of glutathione is 8.72 (see page 8965, bottom of second column equation 4). The specification defines a transduction signal as signals which transport themselves and attached molecules across membranes (page 25, lines 29-30). Further, the specification teaches that peptides share no specific motif or homology other than that they possess a cationic charge (page 26, lines 1-10). Since, each peptide has a positive charge and is linked to a disulfide containing compound with a pKa lower that glutathione, the compounds Pti38 and Pti51a anticipate the claims because they meet the structural limitations required by the claims. Where, as here, the claimed and prior art products are identical or substantially identical, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Whether the rejection is based on "inherency" under 35 USC 102, "*prima facie* obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Keire *et al.* (IDS reference).

Keire *et al.* teach three disulfide containing compounds with a pKa lower than glutathione. Each compounds contains primary amines which are capable of being positively charged (see page 126, Table IV) and thus, serve as transduction signal. As noted above, the specification defines a transduction signal as signals which transport themselves and attached molecules across membranes the signals share no specific motif or homology other than that they possess a cationic charge (page 26, lines 1-10). Since, each compound contains an amine which has a positive charge and is linked to a disulfide containing compound with a pKa lower that glutathione, the compounds taught by Keire *et al.* anticipate the claims because they meet the structural limitations required by the claims. Where, as here, the claimed and prior art products are identical or substantially identical, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Whether the rejection is based on "inherency" under 35 USC 102, "*prima facie* obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Claims 1, 2, 6 and 5 are rejected under 35 U.S.C. 102(e) as being anticipated by Stein *et al.* (6,258,774).

Bulaj *et al.* teach two disulfide linked peptides, Pti38 and Pti51a. Each peptide contains positive charges and have a lower pKa as a consequence (see page 8968, top of second column). The specific pKa is 8.26 for Pti38 and 8.38 for Pti51a (page 8967, Table 1). Szajewski *et al.* teach that the pKa of glutathione is 8.72 (see page 8965, bottom of second column equation 4). The specification defines a transduction signal as signals which transport themselves and attached molecules across membranes (page 25, lines 29-30). Further, the specification teaches that peptides share no specific motif or homology other than that they possess a cationic charge (page 26, lines 1-10). Since, each peptide has a positive charge and is linked to a disulfide containing compound with a pKa lower that glutathione, the compounds Pti38 and Pti51a anticipate the claims because they meet the structural limitations required by the claims. Where, as here, the claimed and prior art products are identical or substantially identical, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Whether the rejection is based on "inherency" under 35 USC 102, "*prima facie* obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Claims 1, 2, 5, 6 and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Stein *et al.* (6,258,774 B1).

Stein *et al.* teach a disulfide containing conjugate for the delivery of therapeutic agents. More specifically, Stein *et al.* teach that nucleotide analogs can be attached as therapeutic agents to a disulfide bond (column 2, lines 40-51) and discuss the use of a HIV tat protein (column 2, lines 52-65). Further, Stein *et al.* teach that numerous cell uptake promoters are known and can be conjugated to 'enhance the ability of the carrier and the therapeutic agent to cross a cell membrane' (column 6, lines 47-49). It is noted that Stein *et al.* provide general guidance for the use of disulfide bonds and do not provide specific teaching for the use of disulfide bonds which are cleaved more rapidly than or have a lower pKa than glutathione, however the specific disulfide cross-linkers used in the examples represent disulfide bonds which meet these limitations (see figure 1-starting compounds and third and final products in reaction scheme). Since, Stein *et al.* teach using a tat protein and nucleic acids as therapeutic agents linked to a disulfide containing compound which by example include disulfides with a pKa lower that glutathione, the compounds taught by Stein *et al.* anticipate the claims because they meet the structural limitations required by the claims.

Claims 1, 5, 6 and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Monahan *et al.* (6,429,200B1).

It is noted that the instant application and US Patent 6,429,200B1 have some common inventors, however the complete inventive entity listed is not the same. The instant application has Rozema and '200 has Hagstrom listed as inventors. Because the instant application and the '200 patent differ by two different inventors the teaching of '200 is being considered to be by another. US Patent '200 provides the same general guidance for the chemical linkage of conjugates through disulfide bonds recited in the instant claims (see for example column 8, lines 5-28). Further, '200 contemplates conjugating gene transfer enhancing agents (column 11, lines 14-21) such as compounds and peptides which aid in the uptake of the compound conjugates. Finally, '200 teaches that a polynucleotide can be attached to the complex for delivery to a cell (column 12, lines 43-48). Additionally, it is noted that the claims of '200 encompass the instant claims specifically reciting that the complex comprise a enhancing ligand (claim 6) and that it contains a disulfide bond (claim 8). Since the only specific reference in '200 to a disulfide bond is exactly the same as instantly claimed, the nature of the disulfide bond set forth in claim 8 is being interpreted in light of this teaching.

Claims 1-6 and 13 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. Specifically, US Patent 6,429,200 B1 provides the same general guidance for the chemical linkage of conjugates through disulfide bonds set forth in the instant claims (see for example column 8, lines 5-28). Further, '200 contemplates conjugating gene transfer enhancing agents (column 11, lines 14-21) such as compounds and peptides which

aid in the uptake of the compound conjugates. In the claims dependent claim 8 specifically recites that the claimed complexes and process of using contain a disulfide bond (column 24). Upon review of the specification the only teaching for any specific form of a disulfide bond is found at column 8, lines 5-28, which is the same as instantly claimed. It appears that both the instant application and '200 have claims encompassing products containing disulfide bonds and methods of use which are the same. It is not clear why the inventors on each of the patent and the application are not the same.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach